NEAR ELIMINATION OF GENITAL WARTS IN AUSTRALIA PREDICTED WITH EXTENSION OF HPV VACCINATION TO MALES

Technical Appendix

Igor A. Korostil[1], MSc; Hammad Ali[1], MPh; Rebecca J. Guy[1], PhD; Basil Donovan[1], MD; Matthew G. Law[1], PhD; David G. Regan[1], PhD

[1] The Kirby Institute, University of New South Wales, Sydney, NSW 2052, Australia

Description of mathematical model

Model structure

We developed a deterministic dynamic compartmental model schematically shown in Figure A1.

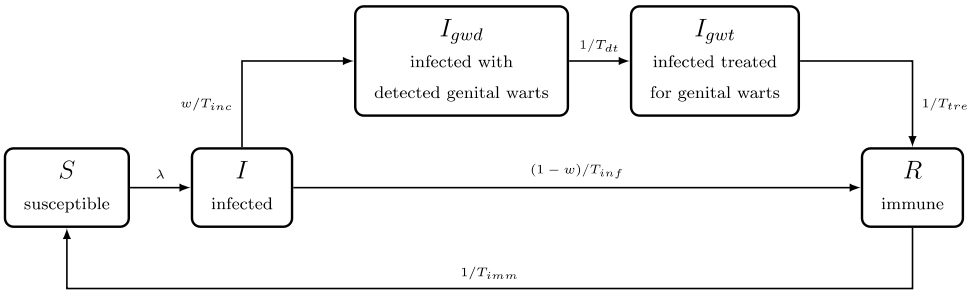

Figure A1. Schematic diagram of the HPV-6/11 mathematical model.

Model parameters

Values for model parameters were, in most cases, gender-specific, as can be seen from Table A1 below.

Parameter, symbol	Value	Unit	Source
Genital warts incubation period, T_{inc}		year	
men	0.5-1.6		[1, 2]
women	0.2-0.6		[3, 4]
Duration of infection, T_{inf}		year	
men	0.4-0.8		[5]
women	0.3-1.0		[6]
Time between detection of genital warts and beginning of their treatment, T_{dt}		year	
men	0.3-0.6		[7, 8]
women	0.1-0.25		[7, 8]
Duration of treatment for genital warts, T_{tre}		year	
men	0.2-0.4		[9]
women	0.15-0.4		[4, 9]
Duration of natural immunity following clearance of infection, T_{imm}		year	
men, women	5.0-45.0		Assumption, no data available
Probability of transmission, β*	0.2-0.5		[10]
Probability to develop genital warts, w			
men	0.3-0.8		[1, 2]
women	0.45-0.8		[4]
Degree of assortativity by age group, ϵ_a [11]	0.1-0.9		Assumption, no data available

Degree of assortativity by age group, ϵ_s [11]	0.1-0.9		Assumption, no data available

Table A1. Model parameters; * this parameter is required to calculate the force of infection λ as described in section "Calculation of the force of infection" .

Key assumptions and limitations

- *The modelled population is heterosexual only.*
  This simplification was made due to the lack of sufficient data on sexual behaviour of men who have sex with men (MSMs) in Australia. MSM are a high risk group in terms of HPV transmission, and comprise a non-negligible proportion of Australian population [12]. Not accounting for MSM in our model may be a substantial limitation;
- *The size of the population is assumed to remain constant. Immigration or temporary visitors are not taken into account.*
  According to the Australian Bureau of Statistics (ABS), Australian population has been growing [13], and this growth has been largely attributable to migrants from overseas. Their number, however, is relatively small as compared with the entire Australian population, and sexual behaviour of migrants has not been captured in any way in the Australian Study of Health and Relationships (ASHR) data that we use in our study. We therefore accepted this apparent limitation, the importance of which is difficult to gauge.
- *No mortality.*
  Individuals simply leave the model at an age that they are assumed to no longer be sexually active
  We consider it acceptable to make this assumption because of the low mortality rates reported by Australian Bureau of Statistics for the age-band in which it is assumed that people are sexually active [14]. Mortality to HPV-6/11 was not included as its existence in doubtful.
- *The population comprised equal numbers of males and females in all age groups.*
  This was assumed for simplicity based on ABS data [13].
- *Sexual activity is assumed to commence at age 13 in both males and females.*
  While data on sexual behaviour in young people in Australia is scarce, we have made this assumption based on some previously published findings [15, 16] .
- *Interaction between HPV types 6 and 11 is assumed not to occur, i.e. current or prior infection with one type has neither a synergistic or antagonistic impact on acquisition or natural history of infection with the other.*
  There have been no studies, to our knowledge, conclusively confirming any practically relevant interaction between these types.
- *Types 6 and 11 are treated as a single "combined" type.*
  This assumption is based on the similarity in model parameter values for the two types and the fact that we calibrated the HPV-6/11 model to data contributed to by both types. As discussed in [17], combining HPV types in transmission models may potentially lead to incorrect conclusions . We would like to stress, however, that this issue was identified when combining

HPV types 16 and 18 and then calibrating combined 16/18 type to a combined "HPV-16 and 18" prevalence. This is a different scenario from ours: we calibrate our model to genital warts incidence, and genital warts are caused to by both HPV type 6 and type 11. It may be argued that HPV-6 contributes to genital warts to a much larger extent than HPV-11, so it might make sense, in principle, to discuss "genital warts caused by HPV-11 only" and "genital warts caused by HPV-6 only". However, given that the data we calibrate to is for genital warts in general and is not stratified by the causal HPV type, we did not consider it necessary to investigate this issue.

- *Vaccine coverage is assumed to be 80% for females (female-only vaccination) and 80% for males (when a male vaccination is introduced).* This assumption was based on the available coverage data [18] for the ongoing female-only vaccination program. The equally high coverage for males was assumed because males would be vaccinated at schools just as the 12 y.o. females currently are, and so it would be reasonable to expect that the coverage achieved should be very comparable.
- *The vaccine (Gardasil) is assumed to be prophylactic and not therapeutic.* This is based on the available reports [19].
- *Vaccination does not trigger replacement of HPV types 6 and 11 with other HPV types contributing to genital warts.*
  While we acknowledge that possibility of HPV type replacement due to vaccination is yet to be thoroughly verified, we are not aware of any literature which would directly substantiate replacement of types 6 and 11. Moreover, there has been some recently presented evidence that the replacement in question does not occur [20].
- *Vaccine protection is life-long.*
  This is based on the previously discussed arguments [21, 22] that in view of the reported duration of protection amounting to at least five years [23] and an apparent existence of a post-vaccination immune memory [24] it is reasonable to assume the life-long protection because even if it was not life-long as such, it could be maintained at an appropriate level by boosters.
- *Sexual behaviour is described in the model based on the results of Australian Study of Health and Relationships (ASHR).*
  We mention this as a potential limitation to acknowledge that the ASHR had a number of limitations (see [12]). Nonetheless, it currently remains the most representative sexual behaviour survey conducted in Australia.

Population stratification

The heterosexual Australian population was stratified in the model as specified in Table A2 below.

Strata	Notation	Possible values
Gender	g	1 (males, 'M') and 2 (females, 'F')
Sexual activity group	s	1,2,3 or 4 (see Table)
Age group	a	1 (12 year olds, '12'), …, 53 (64 year

		olds, '64')
State	i	1 (S), 2 (I), 3(R), 4(I_{gwd}), 5(I_{gwt})
Sexually active	k	1 (active, 'act') or 2 (inactive, 'inact')
Vaccinated	v	1 (vaccinated, 'V') or 2 (unvaccinated, 'U')

Table A2. Stratification of the modelled population.

Model equations

A current state of the model is described by a multi-dimensional array $X(g, s, a, i, k, v)$ with entries indexed as shown in Table A2. This array contains the number of individuals in any subpopulation selected based on the implemented stratification. For example, $X(M, 2,13, R, act, V) = X(1,2,2,3,1,1)$ contains the number of males in sexual activity group 2 who are aged 13, are immune, sexually active and vaccinated. Let us use a colon to denote "any values from the allowed range", so that "$X(M, :, :, R, act, V) = \cdots$ " means *"for any sexual activity group s and age group a* $X(M, s, a, R, act, V) = \cdots$*".*
Evolution of the model states in time is then described by the following system of ordinary nonlinear differential equations:

$$\frac{d}{dt}X(M,:,:,S,act,:) = \frac{1}{T_{imm,m}}X(M,:,:,R,act,:) - \lambda(M,:,:,S,act,:)X(M,:,:,S,act,:),$$

$$\frac{d}{dt}X(F,:,:,S,act,:) = \frac{1}{T_{imm,f}}X(F,:,:,R,act,:) - \lambda(F,:,:,S,act,:)X(F,:,:,S,act,:)$$

$$\frac{d}{dt}X(M,:,:,I,act,:) = \lambda(M,:,:,S,act,:)X(M,:,:,I,act,:) - \left(\frac{w_m}{T_{inc,m}} + \frac{1-w_m}{T_{inf,m}}\right)X(M,:,:,I,act,:),$$

$$\frac{d}{dt}X(F,:,:,I,act,:) = \lambda(F,:,:,S,act,:)X(F,:,:,I,act,:) - \left(\frac{w_f}{T_{inc,f}} + \frac{1-w_f}{T_{inf,f}}\right)X(F,:,:,I,act,:)$$

$$\frac{d}{dt}X\big(M,:,:,I_{gwd},act,:\big) = \frac{w_m}{T_{inc,m}}X(M,:,:,I,act,:) - \frac{1}{T_{dt,m}}X\big(M,:,:,I_{gwd},act,:\big),$$

$$\frac{d}{dt}X\big(F,:,:,I_{gwd},act,:\big) = \frac{w_f}{T_{inc,f}}X(F,:,:,I,act,:) - \frac{1}{T_{dt,f}}X\big(F,:,:,I_{gwd},act,:\big)$$

$$\frac{d}{dt}X\big(M,:,:,I_{gwt},act,:\big) = \frac{1}{T_{dt,m}}X\big(M,:,:,I_{gwd},act,:\big) - \frac{1}{T_{tre,m}}X\big(M,:,:,I_{gwt},act,:\big),$$

$$\frac{d}{dt}X(F,:,:,I_{gwt},act,:) = \frac{1}{T_{dt,f}}X(F,:,:,I_{gwd},act,:) - \frac{1}{T_{tre,f}}X(F,:,:,I_{gwt},act,:)$$

$$\frac{d}{dt}X(M,:,:,R,act,:) = \frac{1-w_m}{T_{inf,m}}X(M,:,:,I,act,:) + \frac{1}{T_{tre,m}}X(M,:,:,I_{gwt},act,:) - \frac{1}{T_{imm,m}}X(M,:,:,R,act,:),$$

$$\frac{d}{dt}X(F,:,:,R,act,:) = \frac{1-w_f}{T_{inf,f}}X(F,:,:,I,act,:) + \frac{1}{T_{tre,f}}X(F,:,:,I_{gwt},act,:) - \frac{1}{T_{imm,f}}X(F,:,:,R,act,:).$$

The first equation states that the change in the number of susceptible males per unit time (the left hand side of the equation) is equal to the number of immune males who become susceptible per unit time minus the number of susceptible males who become infected (and hence move to the infected compartment) per unit time. Other equations should be interpreted in a similar manner.
As can be seen from the equations above and Table A1, parameters in our model are gender-specific (probability of HPV transmission per partnership is an exception), but they are not stratified according to any other attributes.

Sexual mixing and calculation of the force of infection

We calculate the force of infection according to the formulation of sexual mixing and procedure of sexual mixing adjustment proposed by Garnett and Anderson [11]. While it would be excessive to describe in detail all notations and steps involved in the procedure here, we briefly mention some key points below. Essentially, the aim is to generate of a sexual mixing matrix, which we have done using the data presented below (note that PCR stands for 'partner change rate').

	Age groups						
Age (years)	15-19	20-24	25-29	30-34	35-39	40-44	45-59
Relative PCR, per year	5.28	6.06	4.37	2.57	1.61	1.43	1.00

Sexual activity (risk) groups (% of the population in a group)			
1 (60%)	2 (21%)	3 (17%)	4 (2%)
1.00	4.76	24.83	105.67

The overall PCR in Australian population was set equal to 0.437. The data were derived in [25] from the results of the Australian Study of Health and Relationships.
The sexual mixing matrix contains probabilities that an individual of gender g from a sexual activity group s and age group a acquires a new sexual partner of

the opposite gender from a sexual activity group s' and age group a'. These probabilities are defined as

$$\rho_{gss'aa'} = \begin{cases} (\epsilon_a P_{a'}) \times (\epsilon_s P_{s'}), & a \neq a', s \neq s' \\ \left((1-\epsilon_a) + \epsilon_a P_{a'}\right) \times (\epsilon_s P_{s'}), & a = a', s \neq s' \\ (\epsilon_a P_{a'}) \times \left((1-\epsilon_s) + \epsilon_s P_{s'}\right), & a \neq a', s = s' \\ \left((1-\epsilon_a) + \epsilon_a P_{a'}\right) \times \left((1-\epsilon_s) + \epsilon_s P_{s'}\right), & a = a', s = s'. \end{cases}$$

Here $P_{a'}$ ($P_{s'}$) is a proportion of all new sexual partnerships formed by individuals of the opposite gender formed by individuals of the opposite gender from age group a' (sexual activity group s').
Quantities ϵ_a and ϵ_s are degrees of assortativity by age and sexual activity. They vary between 0 and 1. If $\epsilon_a = 0$ sexual mixing is considered fully assortative by age group, which means that sexual partnerships may be established only between individuals from the same age group (see the definition of $\rho_{gss'aa'}$ above). Sexual mixing is fully proportionate by age if $\epsilon_a = 1$. Interpretation of this is that contributions of age to the choice of sexual partners is limited to the level of sexual activity of the opposite gender for each age group ($\rho_{gss'aa'}$ depends only on $P_{a'}$ in terms of age). Similar considerations apply to ϵ_s.

Sexual mixing matrix is used to calculate *absolute* PCRs for each age and sexual activity group (note that we are initially given *relative* PCRs). These are employed to calculate the force of infection.

For example, if we denote $PCR_{(F,1,19,:,act,:)}^{(M,s,a,:,act,:)}$ the annual rate at which (sexually active) females aged 19 in sexual activity group 1 acquire male sexual partners of age a from sexual activity group s, the force of infection on these females will be given by:

$$\lambda(F,1,19,:,act,:) = \sum_{s,a} \beta \cdot PCR_{(F,1,19,:,act,:)}^{(M,s,a,:,act,:)} \left\{X(M,s,a,I,act,:) + X\left(M,s,a,I_{gwd},act,:\right) + X\left(M,s,a,I_{gwt},act,:\right)\right\} / \sum_i X(M,s,a,i,act,:).$$

Here $\left\{X(M,s,a,I,act,:) + X\left(M,s,a,I_{gwd},act,:\right) + X\left(M,s,a,I_{gwt},act,:\right)\right\} / \sum_i X(M,s,a,i,act,:)$ is HPV prevalence in males of age a from sexual activity group s, and β is the probability of HPV transmission per partnership (see Table 1A).

Implementation of ageing

Ageing in our model happens instantaneously at the end of each year:

$$X(:,:,a,:,:,:) = X(:,:,a-1,:,:,:), \quad a = 2,3,\ldots,53.$$

Note that this implies that individuals from the last age group, group 53, simply disappear each year. In fact, this is exactly the case as we assume they leave the sexually active population and hence the model. As for the first age group, not covered by the formula, we place there the susceptible, sexually inactive 12 y.o. individuals who enter the model. The number of these individuals is equal to the

number N_{53} of those who should exit the model, divided into sexual activity groups as given in Table 2 and equally divided between males and females:

$$X(:,1,1,S,:,:) = \frac{0.6 \cdot N_{53}}{2},$$
$$X(:,2,1,S,:,:) = \frac{0.27 \cdot N_{53}}{2},$$
$$X(:,3,1,S,:,:) = \frac{0.11 \cdot N_{53}}{2},$$
$$X(:,4,1,S,:,:) = \frac{0.02 \cdot N_{53}}{2}.$$

Implementation of vaccination: an example

It is assumed that vaccination is carried out at a constant rate which we denote r. Suppose that our aim is to vaccinate $VC\%$ of 12 y.o. sexually inactive females, who are, of course, susceptible, during a year starting at $t = 0$ and ending at $t = 1$. This can be expressed by the following boundary value problem:

$\frac{d}{dt}X(F,:,12,S,inact,V) = rX(F,:,12,S,inact,U)$

$\frac{d}{dt}X(F,:,12,S,inact,U) = -rX(F,:,12,S,inact,U)$

$X(F,:,12,S,inact,U) = U_0,\ X(F,:,12,S,inact,V) = 0$ at $t = 0$

$X(F,:,12,S,inact,U) = \left(1 - \frac{VC}{100}\right)U_0$, $X(F,:,12,S,inact,V) = \left(\frac{VC}{100}\right)U_0$ at $t = 1$.

Solving for r we obtain

$$r = Log\ \left(1 - \frac{VC}{100}\right).$$

Implementation of catch-up: an example

Suppose we want to vaccinate VC=32% of females who are 18 y.o. in 2007 over two years (2007 and 2008). We also know that $VC_1 = 11\%$ of these females were vaccinated in 2007. Then we have to make sure that next year, in 2008, we vaccinate VC_2 unvaccinated 19 y.o. females so that $VC \cdot U_{18,2007} = VC_2 \cdot (1 - VC_1) \cdot U_{18,2007} + VC_1 \cdot U_{18,2007}$, and then

$$VC_2 = \frac{VC - VC_1}{1 - VC_1}.$$

The catch-up campaign was implemented using the coverage (2-dose) shown in Table A3 below.

Age (years)	Time of vaccination	Dose 1 (%)	Dose 2 (%)	Dose 3 (%)
12	From 04/2007, each year	83	80	73
13-15	2007	42	40	36
	2008	42	40	36
	Total vaccine coverage	84	80	72
16-17	2007	41	38	33
	2008	41	38	33
	Total vaccine coverage	82	76	66

18-19	2007	13	11	8
	2008	26	21	15
	Total vaccine coverage	39	32	23
20-26	2007	10	8	6
	2008	21	17	12
	2009	21	17	12
	Total vaccine coverage	52	42	30

Table A3. Australian female HPV vaccination coverage by age as of March 2011.

Calculation of genital warts incidence

Genital warts incidence during a specified time period $[t_0, t_1]$ is the number of new genital warts diagnoses during this period:

$$[GW\ incidence]_{t_0}^{t_1} = \int_{t_0}^{t_1} \frac{1}{T_{dt}} I_{gwd}\,(t)dt \approx \frac{1}{T_{dt}}(t_1 - t_0)\frac{I_{gwd}(t_1) + I_{gwd}(t_0)}{2}$$

where we applied the trapezoidal rule as follows

$$\int_{t_0}^{t_1} I_{gwt}(t)dt \approx (t_1 - t_0)\frac{I_{gwd}(t_1) + I_{gwd}(t_0)}{2}$$

Model calibration

Our model was calibrated to the age specific Australian genital warts incidence data [26] using Bayesian methodology described in detail in [27]. The data are shown in Figure A2 as mean values ('reported mean') with 95% confidence intervals (whiskers). The simulated mean values are shown as circles ('simulated mean') and 95% confidence intervals (grey areas).

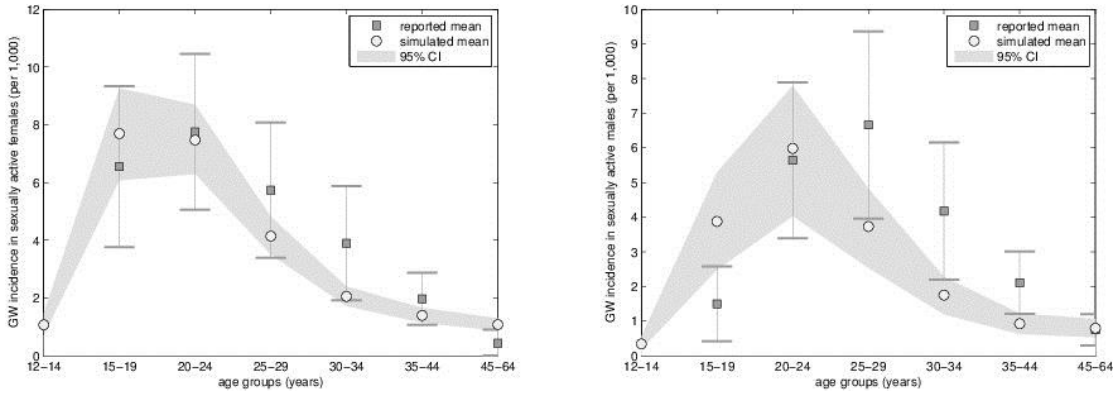

Figure A2. The fit produced by our model to the available age-specific Australian genital warts incidence data.

References

1. Anic GM, Lee JH, Stockwell H, Rollison DE, Wu Y, Papenfuss MR, Villa LL, Lazcano-Ponce E, Gage C, Silva RJ *et al*: Incidence and human papillomavirus (HPV) type distribution of genital warts in a multinational cohort of men: the HPV in men study. *Journal of Infectious Diseases* 2011, 204(12):1886-1892.
2. Arima Y, Winer RL, Feng Q, Hughes JP, Lee SK, Stern ME, O'Reilly SF, Koutsky LA: Development of genital warts after incident detection of human papillomavirus infection in young men. *Journal of Infectious Diseases* 2010, 202(8):1181-1184.
3. Garland SM, Steben M, Sings HL, James M, Lu S, Railkar R, Barr E, Haupt RM, Joura EA: Natural history of genital warts: analysis of the placebo arm of 2 randomized phase III trials of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine. *Journal of Infectious Diseases* 2009, 199(6):805-814.
4. Winer RL, Kiviat NB, Hughes JP, Adam DE, Lee SK, Kuypers JM, Koutsky LA: Development and duration of human papillomavirus lesions, after initial infection. *Journal of Infectious Diseases* 2005, 191(5):731-738.
5. Giuliano AR, Lu B, Nielson CM, Flores R, Papenfuss MR, Lee JH, Abrahamsen M, Harris RB: Age-specific prevalence, incidence, and duration of human papillomavirus infections in a cohort of 290 US men. *Journal of Infectious Diseases* 2008, 198(6):827-835.
6. Trottier H, Mahmud S, Prado JC, Sobrinho JS, Costa MC, Rohan TE, Villa LL, Franco EL: Type-specific duration of human papillomavirus infection: implications for human papillomavirus screening and vaccination. *Journal of Infectious Diseases* 2008, 197(10):1436-1447.
7. Drolet M, Brisson M, Maunsell E, Franco EL, Coutlee F, Ferenczy A, Ratnam S, Fisher W, Mansi JA: The impact of anogenital warts on health-related quality of life: a 6-month prospective study. *Sexually transmitted diseases* 2011, 38(10):949-956.
8. Woodhall SC, Jit M, Soldan K, Kinghorn G, Gilson R, Nathan M, Ross JD, Lacey CJ: The impact of genital warts: loss of quality of life and cost of treatment in eight sexual health clinics in the UK. *Sexually transmitted infections* 2011, 87(6):458-463.
9. Insinga RP, Dasbach EJ, Myers ER: The health and economic burden of genital warts in a set of private health plans in the United States. *Clin Infect Dis* 2003, 36(11):1397-1403.
10. Burchell AN, Coutlee F, Tellier PP, Hanley J, Franco EL: Genital transmission of human papillomavirus in recently formed heterosexual couples. *Journal of Infectious Diseases* 2011, 204(11):1723-1729.
11. Garnett GP, Anderson RM: Balancing sexual partnerships in an age and activity stratified model of HIV transmission in heterosexual populations. *IMA journal of mathematics applied in medicine and biology* 1994, 11(3):161-192.
12. The Australian Study of Health and Relationships. Available at www.ashr.edu.au.
13. Australian Bureau of Statistics. 3101.0 - Australian Demographic Statistics, Jun 2012. Available at www.abs.gov.au
14. Australian Bureau of Statistics. Catalogue number 3302.0 - Deaths, Australia. 2010. Available at www.abs.gov.au
15. Dunne MP, Donald M, Lucke J, Nilsson R, Ballard R, Raphael B: Age-related increase in sexual behaviours and decrease in regular condom use among adolescents in Australia. *International journal of STD & AIDS* 1994, 5(1):41-47.
16. Grunseit AC, Richters J: Age at first intercourse in an Australian national sample of technical college students. *Aust Nz J Publ Heal* 2000, 24(1):11-16.
17. Van de Velde N, Brisson M, Boily MC: Understanding differences in predictions of HPV vaccine effectiveness: a comparative model-based analysis. *Vaccine* 2010, 28(33):5473-5484.
18. Gertig DM, Brotherton JM, Saville M: Measuring human papillomavirus (HPV) vaccination coverage and the role of the National HPV Vaccination Program Register, Australia. *Sexual health* 2011, 8(2):171-178.
19. Gardasil web site. Available at: www.gardasil.com. Accessed 13 September 2012. In.
20. Rositch AF, Hudgens MG, Backes DM, Moses S, Agot K, Nyagaya E, Snijders PJ, Meijer CJ, Bailey RC, Smith JS: Vaccine-relevant human papillomavirus (HPV) infections and future acquisition of high-risk HPV types in men. *The Journal of infectious diseases* 2012, 206(5):669-677.
21. Kulasingam S, Connelly L, Conway E, Hocking JS, Myers E, Regan DG, Roder D, Ross J, Wain G: A cost-effectiveness analysis of adding a human papillomavirus vaccine to the Australian National Cervical Cancer Screening Program. *Sexual health* 2007, 4(3):165-175.
22. Smith MA, Canfell K, Brotherton JM, Lew JB, Barnabas RV: The predicted impact of vaccination on human papillomavirus infections in Australia. *International journal of cancer Journal international du cancer* 2008, 123(8):1854-1863.

23. **Villa LL, Ault KA, Giuliano AR, Costa RL, Petta CA, Andrade RP, Brown DR, Ferenczy A, Harper DM, Koutsky LA *et al*: Immunologic responses following administration of a vaccine targeting human papillomavirus Types 6, 11, 16, and 18.** ***Vaccine*** **2006, 24(27-28):5571-5583.**

24. **Olsson SE, Villa LL, Costa RL, Petta CA, Andrade RP, Malm C, Iversen OE, Hoye J, Steinwall M, Riis-Johannessen G *et al*: Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like particle (VLP) vaccine.** ***Vaccine*** **2007, 25(26):4931-4939.**

25. **Regan DG, Philp DJ, Hocking JS, Law MG: Modelling the population-level impact of vaccination on the transmission of human papillomavirus type 16 in Australia.** ***Sexual health*** **2007, 4(3):147-163.**

26. **Pirotta M, Stein AN, Conway EL, Harrison C, Britt H, Garland S: Genital warts incidence and healthcare resource utilisation in Australia.** ***Sexually transmitted infections*** **2010, 86(3):181-186.**

27. **Korostil IA, Peters GW, Cornebise J, Regan DG: Adaptive Markov chain Monte Carlo forward projection for statistical analysis in epidemic modelling of human papillomavirus.** ***Stat Med*** **2012.**